Nephrotic Syndrome

Introduction

In order to answer a question about glomerular diseases, you need three things: the clinical history, labs to tell you nephritic or nephrotic, and the renal biopsy. If you have two, you should be able to deduce the third. And that's how the test will approach this. You must be able to spot nephrotic syndrome, recognize classic associations of each disease, and then know the biopsy results. "Biopsy results" means the appearance on light microscopy, electron microscopy, and immunofluorescent pattern.

We'll be discussing **five nephrotic syndromes**. In nephrotic syndrome, an initial event causes a derangement of podocytes that causes an increased permeability to protein. The result is **massive proteinuria** (> 3.5 g per day). **Albumin** is a protein, and so albumin is lost. The loss of albumin causes a decrease in oncotic pressure. Low oncotic pressure causes every capillary bed everywhere to have less of a drawing force at the venule end of the capillary bed. This results in **edema**. Part of the syndrome involves **hyperlipidemia** (just remember that and don't worry about the mechanism).

Nephrotic syndrome is: **proteinuria** (3.5 g/day) resulting in a **low serum albumin** (< 3 mg/dL) which provokes **edema**. Oh, and **hyperlipidemia**.

Nephrotic syndrome is caused by **podocyte effacement**. The finding of podocyte effacement on electron microscopy is synonymous with the syndrome and is synonymous with loss of the filtration barrier. The mechanism by which podocytes become effaced varies in each disease. Nephrotic syndrome is not accompanied by renal failure, reduced renal blood flow, or reduced glomerular filtration rate. Therefore, diseases that result in nephrotic syndrome will be diseases of the filtration barrier only. While there will be light microscopy and immunofluorescence findings for each diagnosis, **electron microscopy** will always show podocyte effacement.

That means there is something else that tells you what the disease is. Podocyte effacement may be caused by **immune deposition** diseases that reveal **electron-dense deposits** on electron microscopy and a **characteristic immunofluorescence** (membranous nephropathy, membranoproliferative glomerulonephritis, dense deposit disease). Podocyte effacement may be caused by nonimmune deposition causes (focal segmental glomerulosclerosis, minimal change disease), which will have no deposits and no immunofluorescent pattern, and are separated by their light microscopy findings (none on minimal change disease, and some on FSGS).

The two non-deposition-related disorders are minimal change disease and focal segmental glomerulosclerosis. The three deposition-related disorders are membranoproliferative glomerulonephritis, dense deposition disease, and membranous nephropathy. Those names are long and scary and tend to scare people, so let's simplify them before getting into each one.

Simplifying Nephrotic Syndromes

There are two non-deposition disorders, MCD and FSGS. It is probably the case that MCD is a very mild version of FSGS, and we believe their pathogeneses are likely closely linked. We know for sure, however, that because neither is caused by immune deposition, both will have a normal immunofluorescent pattern.

All nephrotic syndromes will demonstrate podocyte effacement on electron microscopy.

The other three are as easy as 1, 2, 3; or rather, 1, 2, 3embranous. Starting from the capillary and working our way out, the **first** thing we encounter is the endothelial cell fenestrations. Preformed antigen-antibody complexes are small enough to fit through fenestrations, but are either too large or too charged

to get through the basement membrane. That means depositions of these preformed antigen-antibody complexes will accumulate on the endothelial side of the basement membrane, forming subendothelial deposits. The **second** thing we find is the basement membrane. An antigen-antibody complex will not get stuck IN the basement membrane, only on either side of it. Antibodies to antigens that are part of the basement membrane will bind to those antigens. But because they are part of the basement membrane, they will not fall out to form depositions. The **third** thing is the podocyte filtration slit. Antigens are able to get through the basement membrane and fenestrations, but then are too big to fit through the filtration slits. Antibody can also cross the basement membrane, where it forms an antibody-antigen complex, which deposits on the subepithelial side of the basement membrane.

Membranoproliferative glomerulonephritis was formerly type 1 MPGN. Dense deposition disease (DDD) was formerly type 2 MPGN. Membranous nephropathy starts with "m," which we turn on its side to become a 3.

MPGN type 1 is first, so is caused by preformed anti-antibody complexes and will have subendothelial deposits.

DDD (aka MPGN type 2) is second, so is caused by antibodies to antigens of the basement membrane.

3embranous (membranous) is third, so is caused by antigen-antibody complexes and will have subepithelial deposits.

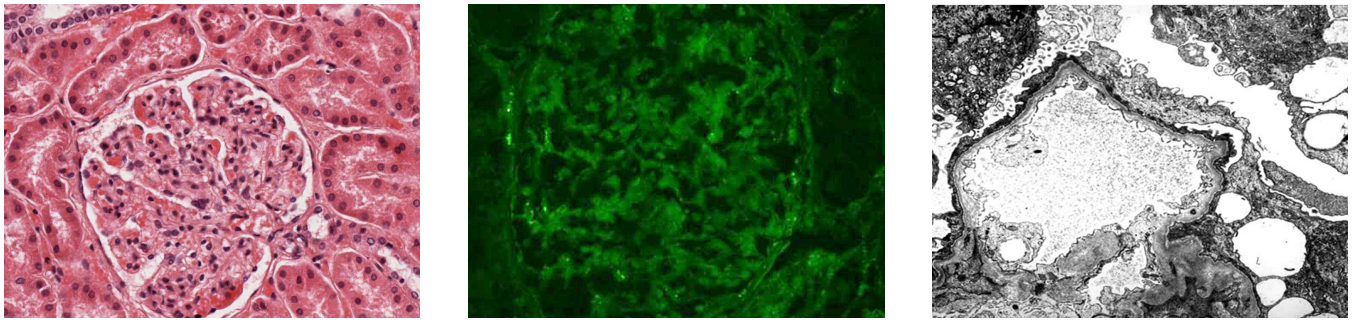
We'll use this advanced organizer as we progress through the remainder of the lesson.

Minimal Change Disease/Nil Disease/Lipoid Nephrosis

MCD is the only **nephrotic syndrome of children** (age 2–6 years). It also demonstrates a **dramatic response to corticosteroid therapy**. Those two features make this diagnosis easy to spot on a licensing exam. In clinical practice, it can be a bit more challenging.

We are certain there is an immune component to the pathogenesis of this disease, because it occurs in children (a developing immune system is more vulnerable to autoimmunity), often follows a viral infection or immunization (inducing the immune system), and responds extraordinarily well to corticosteroids (anti-immune treatment reverses the disease). We are not certain as to the mechanism of autoimmunity, but we know a few things.

There are no immune deposits seen on electron microscopy. If there are no immune deposits, then immunofluorescence for immunoglobulin or complement will be negative. **Immunofluorescence is negative.** If there are no immune deposits, there can't be an enlargement of the basement membrane (no basement membrane thickening). Since it is a nephrotic syndrome, there must be a problem with the filtration barrier only, and so there should be no hypercellularity (neither endocapillary proliferation nor crescents). Both of those statements mean the **light microscopy is normal**. Because it is a nephrotic syndrome, we know that there must be a failure of the podocyte filtration slit, and that means effacement. **The only finding on imaging is effacement of podocytes on electron microscopy.** Podocyte effacement on electron microscopy is synonymous with nephrotic syndrome. It is only when effacement is associated with normal glomeruli on light microscopy that the diagnosis of minimal change disease can be made.



(a) (b) (c)

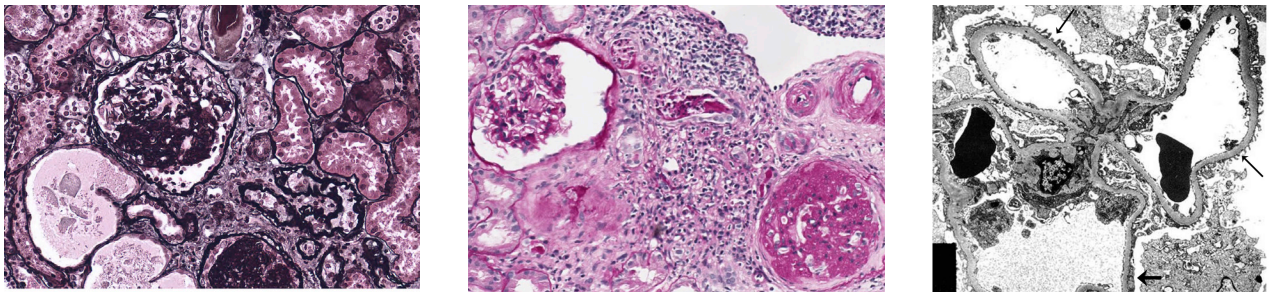
Figure 4.1: Minimal Change Disease
(a) Normal light microscopy without basement membrane thickening or sclerosis. (b) Normal immunflourescence shown to emphasize its negativity. (c) EM shows one capillary loop covered with simplified "fused foot processes." No electron dense deposits are seen.

Kids respond really well to **corticosteroids**. Resolution and complete recovery is the norm, and there is no recurrence. Those patients who do not respond to corticosteroids progress on to FSGS.

Focal Segmental Glomerulosclerosis (FSGS)

FSGS appears to be more like minimal change disease than any of the other diseases discussed in this lesson because FSGS is hallmarked by diffuse **podocyte effacement** but has **no immune-complex deposition**. But unlike minimal change disease, the light microscopy findings are very evident of FSGS. This disease causes only some of the nephrons (**focal**) to have some of their glomeruli (**segmental**) suffer from extracellular protein deposition and subsequent capillary lumen obliteration (**glomerulosclerosis**). We do not know what causes FSGS. We do know that there are some inheritable forms that show gene mutations in proteins that localize to the slit diaphragm, such as nephrin, podocin, and the actin filament connectors. But because primary FSGS is the **most common cause of nephrotic syndrome** in the United States, and none of these patients has this mutation, we know that FSGS can also be caused by something else.

Primary FSGS is either idiopathic or congenital (extremely rare), or comes along with another renal disease, such as HIV nephropathy, heroin nephropathy, or sickle cell disease. **Secondary FSGS** is given to the FSGS that develops as a response to glomerular injury elsewhere, with attempted compensation by the remaining glomeruli.



(a) (b) (c)

Figure 4.2: FSGS
(a) One glomerulus showing incomplete sclerosis. (b) Collapsing variant with antire glomerulus sclerosed (right) and another collapsed (left). (c) This EM is FSGS secondary to reflux nephropathy. It shows slight mesangial expansion, mild thickening of the GBM, no deposits, no hyaline accumulation in these loops, and relatively well preserved foot processes (thin arrows). In general, the "fusion" (thick arrow) occurs much more focally in secondary forms of FSGS when compared to the more diffuse obliteration of foot processes in primary forms.

There is in fact a spectrum of FSGS. It is seemingly as though minimal change disease is on a spectrum with FSGS. Minimal change disease shows only podocyte effacement, no light microscopy changes, and an excellent prognosis. The **FSGS tip variant** shows very little change in the glomeruli on light microscopy. It looks identical to minimal change disease on electron microscopy and responds well to steroids. Conversely, the **FSGS collapsing** variant shows massive change in the glomerulus on light microscopy. There is podocyte proliferation, mesangial proliferation, and a near obliteration of Bowman's space. The only commonality is that all FSGS variants demonstrate podocyte effacement without complex deposition.

In general, FSGS is **unresponsive to steroids** and progresses to ESRD in 50% of patients by year 10. It seems as though once the process starts, nothing can stop its progression.

Light microscopy will show thickening in **some glomeruli** and the affected glomeruli will have **some normal capillary tissue within them**. Electron microscopy will show **effacement of podocytes** in all segments and an **increased mesangial matrix** of sclerotic segments. It is as if two things are going on at once—effacement of the podocytes everywhere and mesangial proliferation causing the sclerosis.

FSGS is said sometimes to present with hematuria, hypertension, and azotemia. These are signs of nephritic syndrome, aren't they? Yes and no. FSGS is progressive, resulting in more and more glomeruli being lost. This induces chronic kidney disease. The chronic kidney disease presents with azotemia, hypertension, and hematuria. See the initial FSGS as only nephrotic syndrome, a more severe form of minimal change disease, and the presentation of hematuria, hypertension, and azotemia as pending end-stage renal disease.

FSGS That Is HIV Nephropathy

HIV nephropathy is caused by an infection with the virus. The pathogenesis is uncertain. The associations are clear. **African Americans** who are infected with **HIV** and are **not on HAART** develop a rapidly progressing **collapsing variant of FSGS**. Associating FSGS with HIV isn't enough. Associate collapsing FSGS with HIV.

Secondary FSGS

Secondary FSGS looks the same as primary FSGS on light microscopy, but represents a process of **progressive fibrosis** that develops in response to many types of renal injury. Some glomeruli. **Compensatory hypertrophy** of the remaining glomeruli develops. The remaining capillaries take on the extra load. The glomerular capillary is already a high-pressure capillary bed. To maintain GFR with the remaining glomeruli, the flow that was formerly delivered to all glomeruli must now be handled by only those that remain. That means each remaining glomerulus receives increased flow. Increasing flow to the remaining glomeruli results in even more hydrostatic pressure. This maintains GFR initially. **Intraglomerular hypertension** induces mesangial cell hyperplasia, extracellular matrix protein deposition, and **podocyte denuding**. The denuding leads to proteinuria. The hyperplasia and matrix deposition lead to sclerosis. At first, only a few glomeruli are affected (focal). At first, only a segment of the glomerulus is affected (segmental). Eventually, the entire glomerulus scleroses, and a vicious cycle that subsequently claims the rest of the glomeruli follows. **Systemic hypertension** develops as the kidneys fail.

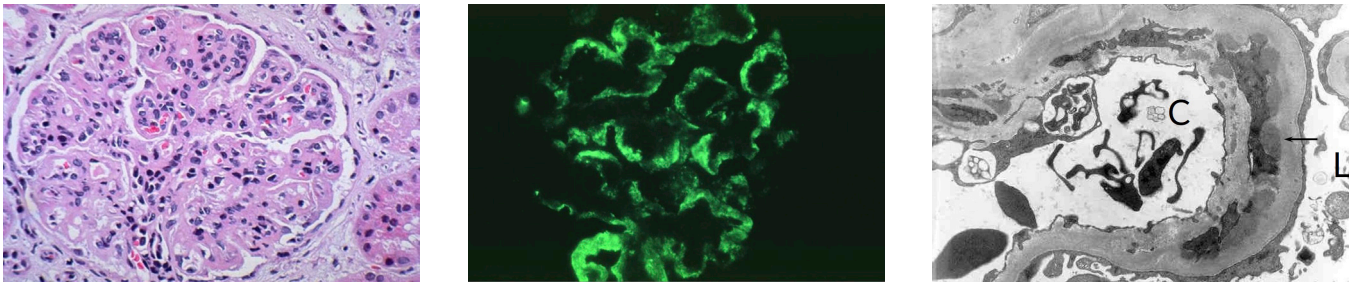
Immune Deposition Nephrotic Syndromes

Remember, this is as easy as *1, 2, 3embranous*. Thus, the diseases are presented in the order of the organizer, MPGN type 1, MPGN type 2 (DDD), and membranous nephropathy.

MPGN type 1 and type 2 were considered the same disease because both cause the same light microscopy changes—endocapillary proliferation from mesangial hyperplasia and splitting of the basement membrane. They were split into MPGN and DDD because electron microscopy and immunofluorescence revealed that although the product of the pathogenesis may have been mesangial hyperplasia and basement membrane splitting, their causes were very different. Mercifully, 3embranous happens to be the third nephrotic syndrome, and it is caused by subepithelial deposits.

Membranoproliferative Glomerulonephritis (MPGN)

In MPGN (formerly MPGN type 1), there are **subendothelial deposits** on electron microscopy. Science has not elucidated what antigen is responsible for these subendothelial deposits. But because they are trapped on the endothelial side of the basement membrane, it is likely that they are from preformed antigen-antibody complex. There is believed to be an association with hepatitis B or hepatitis C. Also on electron microscopy is **mesangial cell infiltration**. Those immune deposits induce mesangial proliferation. The mesangial cells insert themselves between the podocyte and the endothelial cell, **splitting** the basement membrane.



(a) (b) (c)

Figure 4.3: Membranoproliferative Glomerulonephritis
(a) Light microscopy of a glomerulus with predominantly mesangial hypercellularity and occasional polymorphonuclear leukocytes in the capillaries. There is also prominent thickening of the capillary wall, This H&E represents MPGN-1 and DDD. (b) Broad granular staining along glomerular capillary walls for C3. (c) Moving from the capillary lumen (C) out towards the urinary space (L) there is the endothelial cell with fenestrations, new basement membrane (light grey band) mesangial cells (darkest grey) then the subendothelial deposits (circular dark grey, arrow) trapped at what was the original basement membrane (light grey band), then effaced foot processes.

Because the endothelial cells need a basement membrane and the podocytes need a basement membrane, if there is a mesangial cell working its way through the shared basement membrane of the podocyte and endothelial cell, then that one common basement membrane won't do for both cells. Podocytes are epithelial cells of Bowman's space. Endothelial cells are epithelial cells of the capillary. Both epithelial cells need a basement membrane. When there are no deposits, both epithelial cells share a basement membrane. When there are deposits, both make their own membrane. Recall from The Cell, General Physiology #9: *Epithelium*, that the lamina densa is "of the cell" while the lamina propria is "of the extracellular matrix." The podocyte and the endothelial cell each produce the type IV collagen lamina densa, establishing their own basement membrane. Those basement membranes are still relatively very close together. On light microscopy, there will be a "**double-contour,**" "**tram-track**," or "**duplication**" of the basement membrane when stained with PAS, which lights up the basement membrane. Light microscopy is also going to show hypercellularity caused by **mesangial proliferation**.

While the antigen inducing the deposits has not been elucidated, we do know that both **IgG** and **C3** are present on these deposits. Because there are deposits, the immunofluorescent pattern is **granular**. IF shows a granular deposition of both IgG and C3.

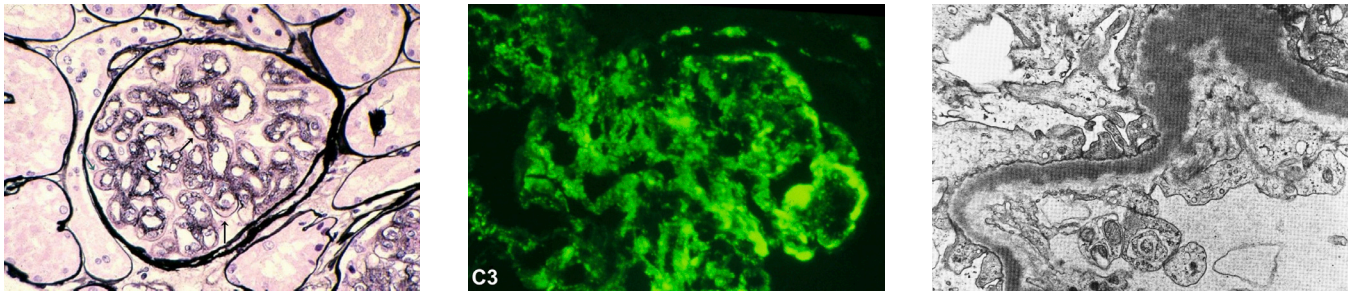
Primary MPGN (occurring on its own) has a poor prognosis. All treatments so far seem to have had no effect. Secondary MPGN occurs in conditions with chronic excess antibody production, such as hepatitis B, hepatitis C with cryoglobulins, and lymphoid malignancies. Treating the condition can halt or even reverse the MPGN.

Dense Deposit Disease (DDD)

DDD was formerly MPGN type 2 because it showed the same light microscopy findings as type 1—endocapillary proliferation (hyperplasia of mesangial cells) and splitting of the basement membrane. When we were able to look closer with electron microscopy, we saw they weren't the same at all. We keep the MPGN type 2 for the organizer "*1, 2, 3embranous*," but we now know how different the pathogenesis is.

Dense deposit disease gets its name from the extremely electron-dense (which means dark gray), **continuous**, **ribbon-like** depositions found **within the basement membrane** on **electron microscopy**. This has the same effect as the mesangial cell splitting the basement membrane in MPGN—a basement membrane than cannot be shared by two different epithelial cells. The podocyte and endothelial cell both do what epithelia do, and each makes its own basement membrane leading to a tram-track or doubling appearance on light microscopy.

DDD shows deposition of **C3 only**. Because the depositions are dense, continuous, and ribbon like, immunofluorescence shows a **linear** pattern that is sometimes granular. Seventy percent of patients with DDD have an autoantibody that has been called **C3 nephritic factor** (C3NeF). This C3NeF is an antibody, an immunoglobulin, that binds to the **alternate pathway's** C3 convertase. The binding of C3NeF to C3 convertase protects C3 convertase from degradation. This favors ongoing C3 convertase activity.



(a) (b) (c)

Figure 4.4: Dense Deposit Disease
(a) Double contoured basement membranes revealed by silver stain, arrows. (Jones' silver methenamine). This silver stain is representative of MPGN-1 and DDD. (b) Immunofluorescence microscopy shows widespread deposition of C3 in a granular linear (c) EM details of the capillary wall. The light grey band at the edge of the urinary space (US) is eclipsed by the dark, continuous band of deposits.

C3 convertase cleaves C3 into C3a and C3b. In the classical pathway, C3 convertase is the combination of C4b and C2a. In the alternate pathway C3b, the thing made by C3 convertase from C3, is able to act as C3 convertase. Yes, you read that correctly. C3 convertase uses C3 to make more C3 convertase. We taught you to not memorize the complement cascade. We do this next bit just to contextualize this paragraph. Words are purposefully left unbolded. Technically, C3 convertase isn't just C3b. It is actually C3bBb (say "see three bee . . . *long pause* . . . bee bee"). C3bBb can cleave C3 into C3a and C3b.

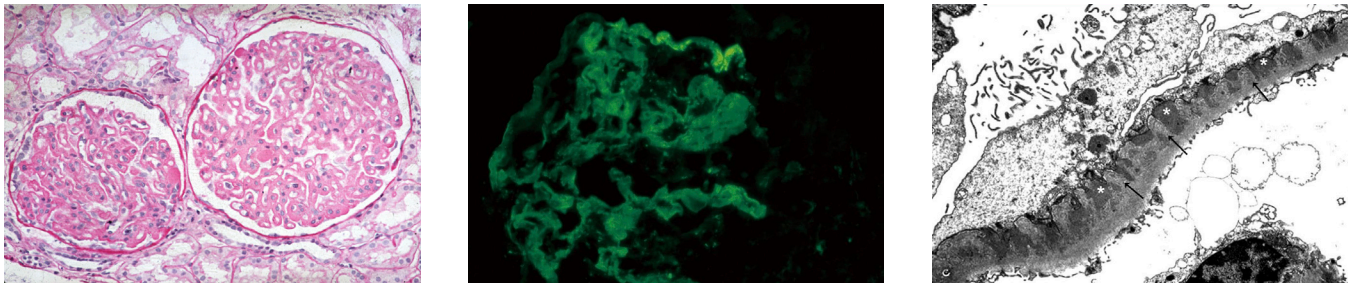
That C3bBb can also cleave C5 into C5a and C5b, acting as a C5 convertase. C5b initiates the MAC attack complex. Regardless of its action (C3 convertase or C5 convertase), C3bBb is usually only very short-lived. With C3NeF antibodies, C3bBb stays active. That means the alternative pathway will be upregulated. This causes the consumption of C3 as well as the consumption of C5–C9. Activation of complement can lead to renal failure. The dense deposits cause nephrotic syndrome from podocyte effacement. The progression of the disease results in renal failure from complement activation.

Ninety percent of patients who receive a transplant will develop dense deposit disease in the transplant. That is because the antigen stimulating the production of C3NeF is likely not within the kidney.

Membranous Nephropathy

This disease was formerly called membranous glomerulonephritis, which confused the hell out of people, as it is not a nephritis (there is no hypercellularity or hematuria). The renaming to "nephropathy" and the convenience of being the third disease and the other one with depositions next to the previous MPGNs, makes memorizing this content much easier.

Being the third, 3embranous nephropathy is caused by **subepithelial** immune deposits that can be seen on electron microscopy. This has been touted in review materials as having a "spike-and-dome" appearance. We think it looks more like the deposits are crashing into the basement membrane with a splash. Since the NBME has gone to extensive lengths to remove buzzwords like "spike-and-dome" from the exam, we recommend you know subepithelial deposits and what they look like. Because it is an immune complex disease and subepithelial deposits are discontinuous, you can expect a **granular immunofluorescence** pattern. Both **IgG and C3** are present (caution, those are the same as in MPGN type 1). Because there are deposits, because the basement membrane has more stuff in it, on light microscopy there will be **thickening of the basement membrane**. Membranous does not induce mesangial hyperplasia or splitting of the basement membrane, only thickening.



(a) (b) (c)

Figure 4.5: Membranous Nephropathy
(a) Light microscopy of a glomerulus with thickened GBM (compare to basement membrane of the tubules nearby. The mesangium is prominent, and there is mild segmental mesangial hypercellularity. (b) Immunofluoresence with IgG Notice the finely granular electron micrograph shows a classical stage II lesion. Numerous, sometimes confluent electron dense deposits in the subepithelial space (asterisks) are separated from each other by "spikes" of matrix material (arrows) that extend from the basement membrane toward the epithelial cells. This gives the appearance of the deposits being partially incorporated into the basement membrane. (c) Fluorescence pattern along the peripheral capillary walls. The mesangial matrix is generally free of deposits.

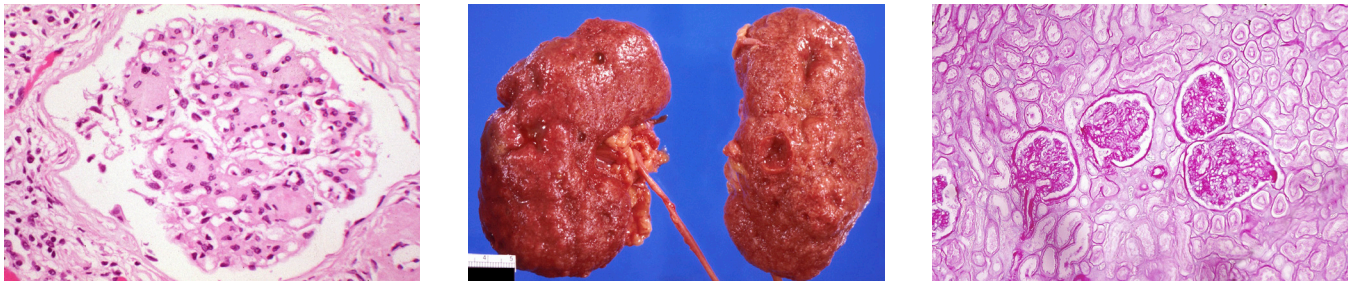
Primary membranous nephropathy is caused by an antibody to the **phospholipase A_2 receptor**. What induces the formation of these autoantibodies is unclear. PLA_2R has a rat equivalent, called megalin. Much of the understanding we have for membranous nephropathy comes from the Heymann model, done on rats. In this model, rats were immunized against megalin. Rats developed subepithelial deposits and nephrotic syndrome. IgG easily diffuses through the basement membrane, binds to megalin, and forms subepithelial deposits. We think that's what happens in humans, IgG to PLA_2R.

Secondary membranous nephropathy is caused by antibody to **planted antigens**. A planted antigen is any protein not of the kidney that gets stuck in the filtration slit. This is the filtration barrier doing a good job. The antigen is in the plasma. Plasma needs to be filtered. The filtration slit prevents large proteins from passing into Bowman's space. Antigen is a protein. Antigen is pushed through the basement membrane but gets stuck at the filtration slit. Seventy-five percent of membranous nephropathy is primary. The most notable secondary causes are **drugs** (penicillamine, captopril, gold, NSAIDs), **infections** (Hep B, Hep C, syphilis), **cancer** (carcinoma of lung and colon), and **lupus**.

Membranous nephropathy does not respond to steroids. Secondary membranous nephropathy has a good prognosis, and usually regresses after the offending agent is removed (treat the Hep C, cure the cancer). Primary membranous nephropathy, caused by autoantibody formation, has a poor prognosis. Those patients transplanted for primary membranous nephropathy will develop membranous nephropathy in the transplanted kidney—the normal PLA_2 receptor the antibody targeted in the first kidney is the same normal PLA_2 receptor the antibody will target in the second kidney.

Special Mention: Diabetic Nephropathy

We'll talk about diabetic nephropathy in the context of diabetes in Endocrine. From a renal perspective, you should be able to recognize the Kimmelstiel-Wilson nodules. Diabetes induces a microangiopathy (capillaries act poorly). Diabetic capillaries are more leaky than normal capillaries. This allows protein to leak out of the capillary into tissue. This is evident in diabetic nephropathy. Outside the capillary can mean either into the urine or into the mesangium. We screen patients with diabetes for nephropathy with a urinalysis, looking for **microalbuminuria** (trace amounts of protein nowhere near nephrotic-syndrome range). If positive, it is evidence that protein is spilling into the mesangium, too. A biopsy is not required for diabetic nephropathy, but if one were obtained, you would see things similar to the words found in the description of nephrotic syndrome. There is **basement membrane thickening**, which can be seen on electron microscopy (no deposits, no immunofluorescence) or on light microscopy. There is **diffuse mesangial proliferation** and deposition of PAS-positive material on light microscopy. The key feature of diabetic nephropathy is the interpapillary glomerulosclerosis, aka Kimmelstiel-Wilson disease. The glomerular lesions take the form of rounded, spherical nodules in the periphery of the glomerulus. The nodules accumulate hyaline material and are acellular. The key is to be able to identify them as diabetes, as hyalinosis, and not as FSGS.



(a) (b) (c)

Figure 4.6: Diabetic Nephropathy
Typical (classic) images of chronic diabetes. (a) Granular cortical surface and on cut section cortical thinning. (b) Chronic diabetic glomerulosclerosis. Kimmelstiel-Wilson lesions in glomerular loops secondary to effusion of protein. (c) PAS stain showing thickening of basement membranes and hyaline arteriolosclerosis of afferent and efferent arterioles, most obviously seen in the glomerulus at the 8 o'clock position.

NEPHROTIC SYNDROMES		
	DISEASE	**CHARACTER**
Non-immune	Minimal Change Disease	Occurs in **children** with **edema** and **anasarca** but who have **no LM** or **IF** changes The only thing that changes is **effacement of podocytes** requiring EM to visualize Responds to steroids
	Focal Segmental Glomerulosclerosis	Common in **African Americans**, AIDS patients, and IV drug users LM: Some parts (segmental) of only some glomeruli (focal) are affected EM: Not needed IF: None Primary FSGS: Unknown pathogenesis Secondary FSGS: Loss of glomeruli causes pressure increases in all others, leads to sclerosis AIDS nephropathy: AIDS patients have the worse **collapsing type**
Immune deposition	MPGN	Path: Unknown antigen, preformed antigen-antibody complexes get stuck on endothelial side EM: Immune-complex deposition is **sub-ENDO-thelial space** IF: Granular **IgG** and **C3** LM: Light microscopy will show mesangial proliferation, tram-tracking of basement membrane
	Dense Deposit	Path: **C3 nephritic factor** (C3NeF) is an antibody that stabilizes **C3 convertase** EM: Immune-complex deposition is within the basement membrane in a **ribbon-like fashion** IF: **Linear** and **C3 only** LM: Light microscopy will show mesangial proliferation, tram-tracking of basement membrane
	Membranous	Path: Autoantibody to filtration slit protein = **phospholipase A_2 receptor**, (primary) Path: Hep B, Hep C, syphilis (infection), penicillamine, gold, captopril (drugs), lung, colon (cancer) EM: Immune-complex deposition is **sub-EPI-thelial space** IF: Granular IF **phospholipase A_2 receptor** LM: Light microscopy will show mesangial proliferation, thickening of capillaries
Systemic	Diabetes	Discussed in Endocrine

Table 4.1